Thyroid Storm

A Review of Cases at University of California, San Francisco

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■ *Retrospective study of the diagnosis and management of the 8 cases of thyroid storm in a series of 400 hyperthyroid patients led to conclusion that thyroid storm is a clinical diagnosis based on a life-endangering illness in a hyperthyroid patient whose hyperthyroidism has been severely exacerbated by a serious precipitating illness, and that storm is manifest by the symptoms of hyperpyrexia, tachycardia and striking alterations in consciousness. No laboratory tests were diagnostic of storm, and the underlying precipitating cause of thyroid storm was the major determinant of survival. Vigorous therapy must include blocking synthesis of thyroid hormones with antithyroid drugs, blocking release of preformed hormone with iodine, meticulous attention to hydration and supportive therapy, as well as correction of precipitating cause of storm. The blocking of the sympathetic nervous system with reserpine or guanethidine or with alpha and beta blocking drugs may be exceedingly hazardous and requires skillful management and constant monitoring in a critically ill patient.*

THYROID STORM IS A LIFE threatening exacerbation of hyperthyroidism. Despite increasing awareness of precipitating factors, metabolic aberrations and treatment, the recent literature still reveals a 20[1] and 60[2] percent mortality.

During the last five years at the medical center at the University of California, San Francisco, eight patients were treated for thyroid storm. When their hospital records were studied, special emphasis was placed on those events which changed thyrotoxicosis into thyroid storm. It became evident that survival was vitally dependent on the antithyroid therapy and also on recognizing and treating the precipitating causes of the storm. Two of the three patients who died during thyroid storm were in "good thyroid control" at the time. The reason for death was that their precipitating illnesses were neither completely recognized nor adequately treated.

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Clinical Material and Methods

The University of California medical center in San Francisco, a 500-bed referral center for the San Francisco Bay Area and Northern California, had approximately 60,000 hospital admissions during the survey period. The 400 hospital records coded for hyperthyroidism between July 1965 and June 1970 were analyzed for thyroid storm. All patients in the survey were either followed by their private physicians or in the Uni-

versity of California thyroid clinic. A diagnosis of thyroid storm was considered to be established when the house staff and attending physicians used the words "thyroid crisis" or "thyroid storm" in the discharge diagnosis. Nine such episodes of storm occurred in eight patients during the study period. Judged by this review, only one hyperthyroid patient not originally diagnosed as having storm met the criteria for storm, and one patient in whom the condition was diagnosed did not meet our criteria of thyroid storm.

Laboratory studies were performed either in the clinical laboratories or the Nuclear Medicine Department of this hospital, or by referral in Clinical Laboratory Associates in Berkeley, California. Accepted normals for protein bound iodine (PBI) are 5 to 8 mg per 100 ml, butanol extractable iodine (BEI) 3.2 to 6.4 mg per 100 ml, true T4 (by displacement) 3.0 to 7.3 mg per 100 ml, 1¼ hour radioiodine uptake less than 15 percent, 5-hour radioiodine uptake 8 to 30 percent, 24-hour radioiodine uptake 15 to 45 percent, T3 uptake 25 to 35 percent, and cholesterol 160 to 260 mg per 100 ml.

Results

Age and Sex. Only 48 (12 percent) of the 400 hyperthyroid patients studied were males. All eight thyroid storm patients were females with an age range from 17 to 60 years and average of 38 years.

Thyroid History. Four of the eight storm patients had a family history of thyroid dysfunction. By either suggestive symptoms or a physician's diagnosis seven of the eight patients had a previous history of hyperthyroidism. The average duration of hyperthyroid symptoms before the onset of thyroid storm was 1.6 years. At the time of admission five of the eight were receiving anti-thyroid medication while two others had recently discontinued antithyroid therapy.

Admitting Diagnosis. The admitting diagnosis of thyrotoxicosis was made in all eight cases, but thyroid storm was the major diagnosis in only five. Subsequently, all eight had storm listed as one of the prominent discharge diagnoses. In six additional patients "impending thyroid storm" was the admitting diagnosis, but in no case did this progress to frank storm and in none of these cases was thyroid storm diagnosed on discharge.

Precipitating Factors. Infection, drug reactions, and vascular syndromes were the most common precipitating events in this series. Each complication contributed to the precipitation in three of the nine cases. Withdrawal of antithyroid therapy contributed to precipitation in two cases, and I^{131} therapy probably in another. (Table 1).

TABLE 1.—*The Incidence of Probable Participating Factors in Eight Cases of Thyroid Storm*

Infection, three cases
Aseptic Meningitis, Cellulitis, Pneumonia
Vascular Syndromes, three cases
Pulmonary emboli, Bowel infarction (vasculitis), Renal infarction
Drug Reaction or Drug Therapy, three cases
Mellaril® (thioridazine); Itrumil® (iothiouracil); propranolol
Discontinuance of Antithyroid Therapy, two cases
Surgical Operation
Subtotal thyroidectomy
Radioactive Iodine Therapy, one case

Symptoms of Thyrotoxicosis. All eight patients had loss of weight (40 pounds in one month and 30 pounds in three months were the most striking). Only four manifested eye signs of exophthalmos, lid lag or decreased convergence at the height of the storm. All eight had hyperpyrexia ranging from 38.5 to 41°, with a mean of 39.8°C; respiratory rate averaged 29 per minute, ranging from 20 to 40.

CNS Signs and Symptoms. All patients had a fine tremor while three complained of myalgia. Four patients were judged psychotic and three others manifested inappropriate affect accompanied by disorientation. Six patients became frankly comatose. Three patients who were responsive but "apathetic" subsequently died.

Cardiovascular Symptoms. The average of heart rates during storm in eight cases was 156 per minute and the range was from 120 to 200. Four patients had atrial fibrillation and one had paroxysmal atrial tachycardia. The average pulse pressure was 78 mm of mercury and the range was from 40 to 100. The diagnosis of congestive heart failure was made in three patients. (Two patients had been treated with propranol, which may have exacerbated the congestive heart failure—a possible drug effect which apparently was not recognized clinically). All three patients with heart failure subsequently died.

Gastrointestinal Symptoms. All eight patients had moderately severe diarrhea, while only four vomited and complained of abdominal pain.

Perforation of the bowel developed in two of those with abdominal pain. Because their gastrointestinal symptoms were attributed to thyroid storm at a time when high doses of corticosteroids were being administered, the diagnosis of perforation was delayed.

Liver Function. Early in storm, the three patients who died had abnormalities of liver function characterized by abnormal prothrombin time, reversed albumin-to-globulin ratio and an elevated bilirubin level. It is of note that all three had some degree of congestive heart failure and that none had SGPT, SGOT, or alkaline phosphatase measurements performed. No significant abnormalities of liver funtion tests occurred in any of the surviving patients.

Renal Function. One dehydrated patient had a depressed creatinine clearance during storm, with reversion to normal by the time of discharge. One of the two patients who died with prerenal azotemia had bilateral renal infarction at postmortem examination.

Thyroid Gland Size and Function Tests. Although results of all thyroid function tests performed during storm were very abnormal, some of the non-storm hyperthyroid patients had test values even more abnormal than the storm patients. The true T4 level in two patients was 17.3, and 17.8 mg per 100 ml (normal below 7.3 mg). In three patients the BEI levels were 15.4, 20 and 14 mg per 100 ml (normal below 6.4 mg), and in these three, cholesterol levels of 140, 104, 102 and 72 mg per 100 ml were recorded during storm. In every patient, test results were more elevated during storm than either before or after storm. Five patients had diffuse enlargement of the thyroid gland, and in two cases nodular enlargement was noted. Only one patient had no apparent increase in the size of the thyroid gland; pathologic examination in that case revealed hyperactivity without enlargement.

Other systems. There were no consistent hematologic, adrenal or carbohydrate metabolism abnormalities noted.

Discussion

What makes the diagnosis of storm? Thyroid storm is classically defined as a dramatic, life threatening, exacerbation of thyrotoxicosis, manifested by high fever, tachycardia out of proportion to the fever, and various other abnormalities of cardiovascular, hepatic and central nervous systems.[1,3,4,5,6,7,8] In the present series the precipitating events of storm and their treatment, not the thyroid abnormalities, apparently determined the survival of the patient. We conclude that thyroid storm is a clinical diagnosis based on a life endangering illness in a hyperthyroid patient whose hyperthyroidism has been severely exacerbated by another serious illness; the symptoms manifested by a storm patient are those of exacerbated hyperthyroidism—tachycardia, fever and striking alterations in consciousness.

What precipitates storm? (Table 1) In this small series, thyroid storm evolved from hyperthyroidism when increased metabolic demands were introduced from extrathyroidal sources, such as infection, pulmonary emboli or drug reactions. Dangerous drug reactions with suspected vasculitis appear to be an unusual but life threatening precipitating cause of storm. Three of our patients had such a reaction, and in one it resulted in bowel infarction. Digitalis intoxication is the only drug reaction documented in the literature as a precipitating cause of storm.[9,10] One hyperthyroid patient presented with headache, which was initially attributed to thyroid storm but subsequently proved to be caused by aseptic meningitis. Another patient had severe cellulitis and another pneumonia. Thus the precipitating events of storm may present serious problems by themselves, and would probably necessitate admission to hospital even if there were no thyroid abnormalities.

Laboratory Findings. Thyroid storm did not appear to be a laboratory diagnosis, and although the thyroid function tests of a storm patient were grossly abnormal, quite a few non-storm hyperthyroid patients had values exceeding those of the storm patients. A poor prognosis in our series of nine cases of storm was associated with severe central nervous system dysfunction, congestive heart failure, and severe abdominal pain. The results of laboratory tests of thyroid function in the nine storm patients improved with therapy.

Therapy of Thyroid Storm. Therapy for this acute medical emergency is aimed at decreasing the production of thyroid hormone, decreasing the release of thyroid hormone, blocking the peripheral action of the thyroid hormones, and care-

fully treating the precipitating cause while making special effort to support vital function.

Iodine may be given orally or intravenously to a critically ill patient, as 1 to 2 grams of sodium iodide, to prevent release of the preformed hormone. This is the most critical proven form of therapy for storm, since it acts immediately to block release of the preformed hormones.

Large doses of antithyroid drugs are usually given to decrease synthesis of thyroid hormones. Large doses of propylthiouracil (1 gram in 24 hours in divided doses every two to four hours given orally or by nasogastric tube) will generally provide adequate therapy. Parenteral therapy is not readily available but can be done by special pharmacy procedures in an extreme emergency. The blockade of thyroid hormone synthesis by the antithyroid drugs is essential since iodine therapy will provide substrate for further hormonal synthesis. These antithyroid drugs will require several days for their effects to be noted. Hence iodine is required for its immediate effect.

Reserpine,[8,11,12] guanethidine[1,13,14] and more recently alpha[15] and beta[16,17,18] blocking drugs have been advocated to (apparently) antagonize the peripheral actions of the excess thyroid hormones. The full benefit of this therapy must be evaluated in the light of its possible risks, such as emotional depression, abdominal pain, postural hypotension, worsening of congestive failure, bronchospasm, and rapid release of histamine or catecholamines. The side effects must be judged in relation to the established effectiveness of more conventional therapy for hyperthyroidism and the precipitating events of the storm. Advocates of catecholamine antagonist medications for storm patients base their use on published reports detailing decreased storm mortality; these reports may be influenced by their authors' definition of storm and consequently the inclusion of patients with less severe thyrotoxicosis. The reports[1,8,11,13,14,15,16] are not controlled and, thus, comparison with previous reports neglects progress in support of vital functions and in treating the precipitating cause of thyroid storm. Other advocates[19] also state reservations as to utilizing sympathetic blockade.

Indiscriminate use of corticosteroids[20] is also to be avoided, since it may alter body defense mechanisms and may so change vital signs of the patient that gauging the effectiveness of therapy is made difficult.

The most critical therapy, as judged by experience in the present series, concerns the treatment of the precipitating events and the support of vital functions. Dehydration must be treated, albeit with care to avoid circulatory overload and hyponatremia. Intravenous glucose and vitamins are advised.[5] Infection must be treated with appropriate antibiotics. Hyperpyrexia should be treated with hypothermic blanket, sponge baths and rectal aspirin, with care taken to avoid rapid changes in temperature and cardiovascular collapse.

In one case in the present series the patient survived what was termed "post thyroidectomy storm" with only supportive therapy. This case would not meet our criteria for storm. Other patients received combined therapy but three patients still died of associated illness or precipitating causes of storm. Two patients died with bilateral renal infarctions. One of these patients had multiple large cerebral infarctions, and the other also had multiple myocardial infarctions, perhaps secondary to drug induced vasculitis.

Comparison with Other Reports

As to the average age of the patients, the high proportion of females, the hyperthyroid symptoms, the laboratory values and the therapy given, the present series did not differ greatly from other reported series.[1,2,7,9,10,21] However, our small series did differ from others in seriousness of the precipitating factors, in the prevalence of central nervous system symptoms, and in the proportion of cases in which storm developed in hyperthyroid patients. Only one of our patients died with storm not under complete control, while in all other series the reports indicate the storm itself rather than the precipitating events, was the cause of death. Our small series had no males, while other series suggest a larger percentage of males in storm compared with those with uncomplicated hyperthyroidism. Our total of 12 percent male hyperthyroid patients does not differ from that of other series. Only 2 percent of our hyperthyroid patients were in storm and only 1 percent had had previous crises, as contrasted with Waldstein's[7] 7 percent incidence of storm in hyperthyroid patients. The mortality in this series, although high, draws attention to details of improving therapy relative to previous studies. The danger of accelerating congestive heart fail-

ure with beta blocking drugs, which occurred in two of our critically ill patients who died, illustrates the possible hazards of nonconventional therapy.

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